Calculating the Economic Benefits of Reductions in Manganese Air Concentrations

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Introduction

The 1990 amendments to the Clean Air Act require the Environmental Protection Agency to provide benefit-cost analyses to accompany standards issued for hazardous air pollutants (HAPs). This exercise is generally conducted in two phases. First, deriving dose-response functions and meshing them with models or measures of human exposure. Second, translating these data into the economic benefits of reduced emissions stemming from reduced health risks. Manganese is among those agents listed as HAPs. It presents a unique challenge and opportunity because it does not fit the typical cancer models and because an assessment can take advantage of a considerable amount of both human and animal data. The model proposed in this article builds on a number of connections among various constituents of neuroscience, clinical neurology, neuropsychology, exposure assessment, and medical economics. Some of the linkages may be no more than suggestive at present, but formulating a model is a useful and intriguing exercise.

Manganese presents a special conumdrum for risk assessment because it is both an essential nutrient and a potent neurotoxicant. Its neurotoxic properties have emerged almost exclusively from inhalation exposures, although some epidemiological data suggest that high concentrations in drinking water may be associated with neurological impairment. Several kinds of occupations expose workers to inhaled manganese, the most prominent being mining, ore-crushing, and ferro-manganese production. Mining for manganese ore provides the best documented association owing to the high levels of MnO_2 dust encountered in the process.

Table 1 lists some of the characteristic signs and symptoms of clinically observed manganese neurotoxicity. Some, like bradykinesia, are also distinguishing signs of Parkinson's disease. Others, like the kind of emotional lability marked by abnormal laughing (and crying), are distinctive for manganese. In South American mining communities familiar with manganese intoxication, such a syndrome has earned the label, "locura manganica," or manganese madness, often viewed as the first stage of the full syndrome of manganese intoxication.

The most suitable animal model for research into manganese neurotoxicity is the nonhuman primate. Because of the unique organization of the primate brain, other animal models, such as rodents, are not as satisfactory, although they may yield useful information about neurochemical processes. Figure 1 depicts these differences as the relationship between dose and measure and shows, roughly speaking, a difference in sensitivity of close to two orders of magnitude between primates and rodents. One factor that may account for some of the discrepancy is the lack of advanced tests for motor function in the rodent studies comparable to the effortful response criterion, based on worker

complaints of excessive fatigue, used by Newland and Weiss (1992) in trained monkeys.

Although the motor signs exhibited by Mn miners correspond in part to those seen in Parkinson's disease (PD), enough differences are apparent to question the widely-held proposition that Parkinson's and manganism are virtually identical. Barbeau (1984) suggested that the syndrome more closely resembled a dystonia than classical PD, a point of view also supported by Pal et al (1999) and others. Neuropathological observations support this distinction. With manganism, the main evidence of degeneration is seen in a brain structure called the globus pallidus, with less severe damage in nearby structures including the striatum (putamen and caudate nucleus) and in the substantia nigra pars reticulata. In contrast, the primary lesions seen in PD lie in the substantia nigra pars compacta and consist of depigmented and missing neurons, viewed as the dominant morphological markers of PD, accompanied by Lewy bodies, which consist of abnormally aggregated proteins found largely in dopaminergic neurons and more recently shown to also contain the protein alpha-synuclein.

Convincing evidence of globus pallidus involvement also comes from magnetic resonance imaging (MRI) data. Because manganese is a paramagnetic metal, it modifies the return of protons to their original orientation after displacement by a strong magnetic field. These shortened times can then be used to produce different degrees of brightness in the calculated image that are related to local manganese concentration. The images and plots published by Newland et al (1989) and Newland and Weiss (1992) show the highest concentrations, in exposed monkey brains. in the vicinity of the globus pallidus. MR images of an arc welder who had been exposed in the process of repairing and recycling railroad track made of manganese steel alloy also showed localized deposition in the globus pallidus (Nelson et al, 1993). Huang et al (1999) compared manganese-exposed workers such as welders with other manual workers and with clerical workers. T1-weighted MR images as evaluated by radiologists confirmed the increased signal intensities in globus pallidus reported by the earlier investigations.

Ingested manganese is closely regulated by the gut. Inhaled manganese bypasses the gut, and can enter the brain in two ways. First, as described by Tjalve and Henriksson (1999), the olfactory pathways provide a direct path into brain tissue. Rats given ^{54}Mn intranasally accumulated the metal in a variety of brain structures, including the basal ganglia. Primates exposed by inhalation to trace amounts of ^{54}Mn showed a rise in brain levels that peaked at about 40 days (Newland et al, 1987). The manganese disappeared from brain much more slowly, with half-lives of 223 to 267 days in the two monkeys studied. ^{54}Mn was detected in the lungs for 500 days after exposure, suggesting that they served as a reservoir for uptake into brain (Figure 2). Although these data may also reflect some storage in bone, as noted by Andersen et al (1999), they indicate the strong possibility that long residence times in the lung provide a continuing

source of brain exposure. This may be a special problem for young children in areas where dense vehicular traffic deposits manganese-laden dust. As with lead (cf., Lanphear et al, 1998), typical children's activities in high dust areas will expose them to elevated levels of both inhaled and ingested manganese, and Dorman et al (2000) have recently shown that neonatal rats administered manganese orally may be at greater risk for Mn-induced neurotoxicity than adult rats.

Most of the data pertaining directly to the benefits issue come from occupational studies. Table 2 gives the details of some of the important studies that attempted to relate exposure to neurobehavioral endpoints. The mean blood concentrations of exposed workers, except for Chia et al (1993), hover near 10 µg/L, with their controls at one-half to two-thirds that value. Chia et al, however, studied a population in Singapore whose dietary habits undoubtedly differed from those in the other studies. Table 3 compares the results of a number of studies based on neurobehavioral endpoints. What is most evident there is the apparent sensitivity of motor function tests to manganese exposure, a result consistent with the evidence showing the main sites of deposition to lie in the basal ganglia, particularly the globus pallidus. Table 4 (Lucchini et al, 1999) offers more recent data from the population studied by Lucchini et al (1995). It too shows that mean control blood values are two-thirds of exposed values, meaning that an elevation of one-third above baseline accounts for the performance differences between the two populations of workers. Also, note the closely overlapping ranges. Figure 3 plots the relationship in this population between air concentration and blood level in the work environment. Two features deserve comment. One is that even negligible air concentrations are associated with blood levels, as noted above, not overwhelmingly different from much higher concentrations. The second is that, at least in these workplaces, the distribution of exposure, as the authors note, is log-normal, with most workers clustered at the low end.

The blood levels determined by Kim et al (1999) lie in about the same range: 14.2 µg/L for exposed workers, 11.7 µg/L for unexposed manual workers, and 11.8 µg/L for clerical workers. Corresponding air levels were 0.53, 0.14, and 0.15 mg/m^3 (cf., Figure 3). Although the 89 exposed workers were largely asymptomatic except for a small group of six with detectable tremor, their MRI scans indicated elevated concentrations of manganese in globus pallidus.

Worker populations present special problems for risk assessment. The healthy worker effect, a notorious confounder in epidemiological investigations, reduces the accuracy with which occupational data can be extrapolated to groups such as children, the elderly, or other especially susceptible populations. Moreover, standards such Threshold Limit Values and Permissible Exposure Limits are based on 8-hour days and 40-hour weeks rather than continuous environmental exposure. To more directly determine potential manganese toxicity in the general population, Mergler et al (1999) undertook a community study in southwest Quebec. The subjects ranged from 20 to 69 years of age and

had not experienced any workplace exposures. The entire study sample of 297 subjects was about equally divided between men and women.

Table 5 presents the blood values. They show slightly higher levels in the women than in the men, but totally overlapping ranges. The investigators administered the most extensive series of neurobehavioral tests ever used to study manganese, and based most of their analyses on a separation of subjects based on blood levels. A value of 7.5 µg/L served as the dividing concentration. Age was chosen as a second dichotomous variable separating subjects below and above 50 years of age.

The neuropsychological measures adopted by Mergler et al (1999) and that documented evidence of adverse effects are listed in Table 6. The first four are indices of motor function and the first three are described at length by Beuter et al (1999). The motor function measures yielded convincing relarionships, but their most interesting features are their dependence on age. Figure 4 displays the interaction between manganese blood level (above or below 7.5 µg/L) and age (above or below 50 years) for the index used to describe performance on a task requiring the subject to alternate strikes with a stylus at two spatially separated targets. This pattern, showing a persuasive influence of age, is consistent with most of the data from this study.

Aging may have played a role in the study reported by Hochberg et al (1996). They undertook to ascertain the late effects of manganese exposure in asymptomatic Chilean miners, relying on devices to measure tremor and fine motor control. The investigators examined 59 individuals aged 50 years or older (mean age, 64.4 years). Twenty-seven exposed miners had been exposed to high levels in the mines for more than 5 years (mean duration, 20.25 years), but exposure had end at least 5 years earlier. Thirty-two controls had never worked in the mines or had experienced only short-term employment. The motor function tests were able to distinguish the performance of exposed miners from that of controls. They concluded, “Chronic asymptomatic Mn exposure results in detectable late-life abnormalities of movement.”

Neurodegenerative diseases, like most other degenerative diseases, are typically diseases of aging, with both incidence and prevalence rising with advancing age. One useful way to contemplate the potential impact of neurotoxic chemicals is to evaluate how they might shift the relationship between prevalence and age. A model of how even small shifts in a population distribution can incur large public health costs is seen in Figure 5. It depicts the consequences of a 3-point or 3% shift in mean IQ score, the kind of shift produced by small elevations in lead exposure. It shows that even that small a shift produces a significant increase in the number of individuals classified as mentally retarded. It incurs massive expenses in remedial care and education, but also produces a significant decrease in the number of individuals in the superior range (e.g., IQ>130). Figure 6 shows that even a 1% leftward shift, or

one IQ point, is a significant societal burden. In its evaluation of the benefits stemming from the removal of lead from gasoline, EPA, basing its calculations on the relationship between IQ score and lifetime earnings, estimated benefits approximating one trillion dollars.

A variation of this logic can be applied to manganese given the assumption that it can contribute to neurodegenerative disease. First, consider Figure 7, which depicts the reduction in nerve cell density with age that occurs in certain brain structures. McGeer et al (1988) plotted the relationship between age and nerve cell number in the substantia nigra (SN). Similar calculations were reported by Fearnley and Lees (1991). A key pathological marker of PD is loss of pigmented neurons in one part of SN. Figure 7 demonstrates that an acceleration of this natural loss by 0.1% annually will, over several decades, produce what might be termed premature aging of this structure. If the natural course of aging produces a loss of 40% by age 73, say, an additional acceleration of 0.1% will incur such a loss about ten years earlier.

Assume exposure to an agent that produces such a superficially minor acceleration. Figure 8 shows the consequences for the prevalence of PD of accelerations of 5 and 10 years respectively. The consequences are hardly minor. Table 7 takes the prevalence figures on which Figure 8 is based, and, from the projected US age distribution (US Census) in 2005, shows the baseline rates of PD and their estimated medical costs, and compares them to what would be expected if the age distribution were to be shifted by five years. The differences are considerable, and would result from an acceleration of functional loss of less than 0.1% annually (see Figure 7).

Would this be a reasonable model for manganese? Or, put another way, what evidence is there to support a contribution by manganese exposure to PD or other neurodegenerative diseases?

One source of evidence is the profile of manganese poisoning, which confirms that it is a powerful neurotoxicant, producing the kinds of clinical signs, some overlapping with Parkinson's disease, listed in Table 1. A second source of evidence comes from detailed studies of both communities and workers indicating that exposed populations displaying no signs of clinical disease can nevertheless be shown to suffer from neuropsychological deficits detected by appropriate testing procedures. But this kind of evidence is not specific to PD.

What is specific to PD, however, is both research and experimental data implicating the central nervous system structures targeted by manganese in PD. To incorporate these results into a benefits analysis first requires some probing into the potential relationship between manganese and neurodegenerative disease. It will be especially illuminating to examine how it might relate to PD because it is a clear example of a relationship with age. As noted earlier, the globus pallidus, on the basis of both chemical analyses and MRI, appears to

accumulate manganese in greater quantities than other basal ganglia structures and is the main site of lesions produced by manganese. Although neuropathology does not indicate manganese-induced damage to the structure directly implicated in PD, the pars compacta of the substantia nigra, a great deal of evidence links its function with the globus pallidus. Both are basal ganglia structures, and functionally joined because the basal ganglia, a collection of nuclei lying below the white matter of cerebral cortex, are intricately coupled. They include the caudate and putamen (striatum), nucleus accumbens, globus pallidus, substantia nigra, and subthalamic nucleus. They are connected to each other by a complex neurochemical and anatomical network consisting of both excitatory and inhibitory pathways. Figure 9 shows neurotransmitter linkages among various basal ganglia structures and emphasizes the lack of isolation among them.

One measure of the critical role played by GP in PD is the burgeoning literature on attenuation of PD symptoms by pallidal surgery or stimulation. Electrical stimulation of the internal pallidum can significantly improve clinical signs, reduce the fluctuations associated with medication such as L-dopa, and permit a reduction in dosage (e.g., Durif et al, 1999). Pallidal surgery is now an accepted method for bringing substantial relief to PD patients (e.g., Fine et al, 2000). In addition, electrophysiological studies indicate a role for the globus pallidus in the resting tremor displayed by PD patients (Lozano et al, 1998). One explanation for the neurobehavioral deficits correlated with manganese exposure comes from these therapeutic efforts. Lombardi et al (2000) reported that lesions in certain pallidal areas induced cognitive impairment, while, in other locations, they produced no effects or even improvement.

One conclusion to be drawn from this interdependence is that what are called extrapyramidal disorders, such as Parkinson’s disease, possess commonalities arising from their intimate and extensive structural and chemical interconnections. Damage to one component of the basal ganglia almost surely is bound to exert influence on functions subserved by other structural components, as in the overlapping symptoms of PD and Alzheimer’s disease. In addition, the disabling effects of pharmacological therapies for PD, such as the dyskinesias resulting from L-dopa, are improved by pallidal stimulation, another source of evidence for the intimate links between GP and SN. One piece of confirmatory evidence comes from Shinotoh et al (1995). They administered manganese to monkeys, evoked clinical signs, and conducted MRI and PET imaging. On the basis of their findings showing both enhanced MRI signal intensity and pathology in globus pallidus, they concluded that, “Chronic manganese intoxication may cause parkinsonism by damaging output pathways downstream to the nigrostriatal dopaminergic pathway. This is consistent with the demonstrated lack of therapeutic response to levodopa.” A further example comes from an experiment with monkeys (Zhang et al, 1999) rendered hemi-parkinsonian by an injection into the right carotid artery of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), originally discovered as a contaminant in

designer drugs that produced parkinsonian signs in drug addicts. Figure 10 shows that monkeys with pallidal damage, observed by MRI, resulting from MPTP were less responsive to the amelioration of PD signs by L-dopa than monkeys lacking evidence of damage.

Insensitivity to therapeutic measures such as L-dopa apparently persists even after MRI signals and tissue concentrations of manganese in blood, urine, scalp hair, and pubic hair return to normal 10 years later (Huang et al, 1998). Unresponsiveness to therapy must also be considered a potential cost of elevated manganese exposure.

One question that remains unresolved involves the different pharmacokinetic behaviors of ingested and inhaled manganese. Ingested manganese is regulated by mechanisms that restrict absorption to low percentages of manganese in the diet (Greger, 1999). Inhaled manganese seems to penetrate the brain far more easily. Olfactory structures, at least in rats, act as a conduit to other areas of the brain (Tjalve and Henriksson, 1999). Vitarella et al (2000), also in rats, reported that, at an air concentration (0.3 mg/m^3) that did not increase blood levels, manganese concentrations rose in olfactory bulb, striatum, and lung after 14 daily exposures. Elevated red cell and plasma manganese concentrations rose only in rats exposed to 3 mg/m^3 subjected to 10 daily exposures. The data from Newland et al (1987) depicted in Figure 2 suggest that the lung, as noted before, may act as a reservoir to produce prolonged elevations of manganese in brain. When examined together, these findings suggest the possibility that relatively modest elevations in manganese air concentrations may increase brain levels without a corresponding reflection in blood levels.

Such a possibility might account for why both community surveys (Mergler et al, 1999) and studies of worker populations (e.g., Apostoli et al, 2000; Kim et al, 1999) indicate that relatively minor increments in manganese blood levels are associated with significant diminutions in neurobehavioral function. If these functional indices are assumed to reflect deficits in brain function, and if we pair these deficits with the recognized declines in brain compensatory capacity associated with aging, slight elevations in airborne manganese might produce a small, but medically and economically significant shift to an earlier onset of neurodegenerative diseases such as Parkinson's disease.

"Small" and "significant" need to be seen in context. An aging population is beginning to confront us with difficult medical and economic choices, and the most overwhelming problem is certain to be neurodegenerative diseases. In evaluating the potential contributions of environmental neurotoxicants to this problem, a simple calculation will prove illuminating. If the entrance of 30 patients into institutional care is delayed by one year, the savings amount to over one million dollars.

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